Special Communication

CDC Guideline for Prescribing Opioids for Chronic Pain—United States, 2016

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IMPORTANCE Primary care clinicians find managing chronic pain challenging. Evidence of long-term efficacy of opioids for chronic pain is limited. Opioid use is associated with serious risks, including opioid use disorder and overdose.

OBJECTIVE To provide recommendations about opioid prescribing for primary care clinicians treating adult patients with chronic pain outside of active cancer treatment, palliative care, and end-of-life care.

PROCESS The Centers for Disease Control and Prevention (CDC) updated a 2014 systematic review on effectiveness and risks of opioids and conducted a supplemental review on benefits and harms, values and preferences, and costs. CDC used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework to assess evidence type and determine the recommendation category.

EVIDENCE SYNTHESIS Evidence consisted of observational studies or randomized clinical trials with notable limitations, characterized as low quality using GRADE methodology. Meta-analysis was not attempted due to the limited number of studies, variability in study designs and clinical heterogeneity, and methodological shortcomings of studies. No study evaluated long-term (≥1 year) benefit of opioids for chronic pain. Opioids were associated with increased risks, including opioid use disorder, overdose, and death, with dose-dependent effects.

RECOMMENDATIONS There are 12 recommendations. Of primary importance, nonopioid therapy is preferred for treatment of chronic pain. Opioids should be used only when benefits for pain and function are expected to outweigh risks. Before starting opioids, clinicians should establish treatment goals with patients and consider how opioids will be discontinued if benefits do not outweigh risks. When opioids are used, clinicians should prescribe the lowest effective dosage, carefully reassess benefits and risks when considering increasing dosage to 50 morphine milligram equivalents or more per day, and avoid concurrent opioids and benzodiazepines whenever possible. Clinicians should evaluate benefits and harms of continued opioid therapy with patients every 3 months or more frequently and review prescription drug monitoring program data, when available, for high-risk combinations or dosages. For patients with opioid use disorder, clinicians should offer or arrange evidence-based treatment, such as medication-assisted treatment with buprenorphine or methadone.

CONCLUSIONS AND RELEVANCE The guideline is intended to improve communication about benefits and risks of opioids for chronic pain, improve safety and effectiveness of pain treatment, and reduce risks associated with long-term opioid therapy.

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Clinicians should review PDMP data for opioids and other controlled medications patients might have received from additional prescribers to determine whether a patient is receiving high total opioid dosages or dangerous combinations (eg, opioids combined with benzodiazepines) that put him or her at high risk for overdose. Ideally, PDMP data should be reviewed before every opioid prescription. This is recommended in all states with well-functioning PDMPs and where PDMP access policies make this practicable (eg, clinician and delegate access permitted), but it is not currently possible in states without functional PDMPs or in those that do not permit certain prescribers to access them.

If patients are found to have high opioid dosages, dangerous combinations of medications, or multiple controlled substance prescriptions written by different clinicians, several actions can be taken to augment clinicians' abilities to improve patient safety:

- Clinicians should discuss information from the PDMP with their patient and confirm that the patient is aware of the additional prescriptions.
- Clinicians should discuss safety concerns, including increased risk for respiratory depression and overdose, with patients found to be receiving opioids from more than 1 prescriber or receiving medications that increase risk when combined with opioids (eg, benzodiazepines).
- Clinicians should avoid prescribing opioids and benzodiazepines concurrently whenever possible. Clinicians should communicate with others managing the patient to discuss the patient's needs, prioritize patient goals, weigh risks of concurrent benzodiazepine and opioid exposure, and coordinate care.
- Clinicians should calculate the total MME/d for concurrent opioid prescriptions. If patients are found to be receiving high total daily dosages of opioids, clinicians should discuss their safety concerns with the patient, consider tapering to a safer dosage, and consider offering naloxone.
- Clinicians should discuss safety concerns with other clinicians who are prescribing controlled substances for their patient.
- Clinicians should consider the possibility of a substance use disorder and discuss concerns with their patient.
- If clinicians suspect their patient might be sharing or selling opioids and not taking them, clinicians should consider urine drug testing to assist in determining whether opioids can be discontinued without causing withdrawal. A negative drug test for prescribed opioids might indicate the patient is not taking prescribed opioids, although clinicians should consider other possible reasons for this test result.

Clinicians should not dismiss patients from their practice on the basis of PDMP information. Doing so could result in missed opportunities to provide potentially lifesaving information and interventions.

10. When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs. (Recommendation category: B; evidence type: 4)

Prior to starting opioids for chronic pain and periodically during opioid therapy, clinicians should use urine drug testing to assess for prescribed opioids as well as other controlled substances and illicit drugs that increase risk for overdose when combined with opioids, including nonprescribed opioids, benzodiazepines, and heroin.

In most situations, initial urine drug testing can be performed with a relatively inexpensive immunoassay panel for commonly prescribed opioids and illicit drugs. Patients prescribed less commonly used opioids might require specific testing for those agents. The use of confirmatory testing adds substantial costs and should be based on the need to detect specific opioids that cannot be identified on standard immunoassays or on the presence of unexpected urine drug test results. In addition, clinicians should not test for substances for which results would not affect patient management or for which implications for patient management are unclear. Clinicians should be familiar with the drugs included in urine drug testing panels used in their practice and should understand how to interpret results for these drugs. Before ordering urine drug testing, clinicians should explain to patients that testing is intended to improve their safety, should explain expected results (eg, presence of prescribed medication and absence of drugs, including illicit drugs, not reported by the patient), and should ask patients whether there might be unexpected results. Clinicians should discuss unexpected results with the local laboratory or toxicologist and with the patient. Discussion with patients prior to specific confirmatory testing can sometimes yield a candid explanation of why a particular substance is present or absent and obviate the need for expensive confirmatory testing on that visit. If unexpected results are not explained, a confirmatory test using a method selective enough to differentiate specific opioids and metabolites (eg, gas or liquid chromatography/mass spectrometry) might be warranted to clarify the situation.

Clinicians should not dismiss patients from care based on a urine drug test result. This could have adverse consequences for patient safety, including missed opportunities to facilitate treatment for substance use disorder.

11. Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible. (Recommendation category: A; evidence type: 3)

Although there are circumstances when it might be appropriate to prescribe opioids to a patient receiving benzodiazepines (eg, severe acute pain in a patient taking long-term, stable low-dose benzodiazepine therapy), clinicians should avoid prescribing opioids and benzodiazepines concurrently whenever possible. In addition, given that other central nervous system depressants (eg, muscle relaxants, hypnotics) can potentiate central nervous system depression associated with opioids, clinicians should consider whether benefits outweigh risks of concurrent use of these drugs. Clinicians should check the PDMP for concurrent controlled medications prescribed by other clinicians and should consider involving pharmacists and pain specialists as part of the management team when opioids are co-prescribed with other central nervous system depressants. When patients require tapering of benzodiazepines or opioids to reduce risk of fatal respiratory depression, it might be safer and more practical to taper opioids first. Clinicians should taper benzodiazepines gradually if discontinued because abrupt withdrawal can be associated with rebound anxiety, hallucinations, seizures, delirium tremens, and, in rare cases, death. If benzodiazepines prescribed for anxiety are tapered or discontinued, evidence-based psychotherapies (eg, CBT) and specific antidepressants or other nonbenzodiazepine medications approved for anxiety should be offered. Clini-

The ASAM Principles of Addiction Medicine

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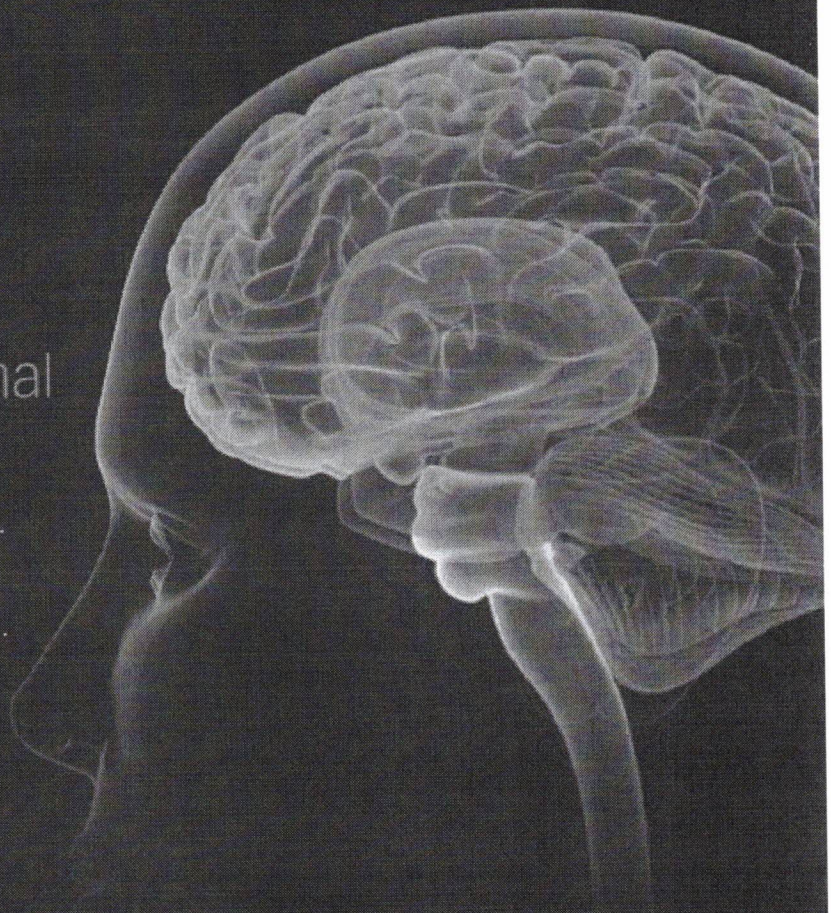

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ETHICAL ISSUES IN ALCOHOL AND DRUG TESTING

Beauchamp and Childress have developed a widely used approach to bioethical reasoning. Their four principles—beneficence, nonmaleficence, justice, and respect for autonomy—provide a lens through which to examine the ethical aspects of clinical drug testing (75).

Beneficence refers to the ethical principle that clinicians are obliged to act for the benefit of their patients. Drug testing is a diagnostic tool that, when integrated with other information, can be helpful in diagnosing, or monitoring the status of, substance use disorders. As with every diagnostic test, the result should be used to inform medical care and not to punish patients for displaying signs of a medical disorder. Additionally—and especially for patients in the early stages of substance use disorder treatment—appropriate drug test results can provide positive reinforcement, thereby supporting their recovery efforts (76).

Nonmaleficence refers to the ethical principle that clinicians should refrain from acts that may harm their patients. Drug testing poses a number of potential harms, the most important of which accrue from errors in the ordering of tests and interpretation of test results and from inappropriate responses to test results (76). Errors of ordering and interpretation are commonplace and generally result from inadequate education (77–79). With regard to the ordering of drug tests, the clinician should be knowledgeable about the composition of the drug test panel and the analytical limitations of the test.

Drug tests are never "general" tests for ruling out the presence of one or more of the ever-increasing number of drugs with a potential for abuse. Rather, drug tests, regardless of the analytical technique, are directed toward a panel—and often a very limited panel—of drugs. Thus, the clinician must be certain that the drugs of interest are represented on the panel. Similarly, unskillful interpretation of test results, discussed in another section of this chapter, can result in false accusations of drug abuse or, conversely, in accusations of nonadherence to prescribed controlled substance regimens, with resulting negative consequences for patients.

Inappropriate, punitive clinical responses to drug test results can have important and enduring consequences for patients. Such responses may diminish the patient's trust in the clinician and may harm the therapeutic relationship. The most draconian response to an inappropriate drug test result—discharging the patient from a practice—is only rarely an acceptable option. Such acts foreclose opportunities to discuss the reason for the test results, to determine whether there might be a substance use disorder (or relapse), and, if so, to initiate treatment or referral. Furthermore, it may precipitate uncomfortable and sometimes dangerous withdrawal syndromes or drive the patient to seek controlled substances from emergency rooms or nonmedical sources (76).

Finally, as medical records are increasingly likely to follow patients through the healthcare system, misinformation (such as an incorrect interpretation of test results, characterizing patients as nonadherent with prescription instructions, or misdiagnosing patients as having substance use disorders on the basis of drug test results) has the potential to negatively affect the care patients receive from future clinicians and may have consequences for insurance coverage (76).

The ethical principle of *justice* dictates that patients be treated fairly and equitably. This means that drug testing must be driven by patient-specific considerations, such as the risk of development or recurrence of a substance use disorder. There is no empirical or ethical justification for drug testing on the basis of patient ethnicity, race, religion, sexual orientation, or likeability (76).

The fourth ethical principle, *respect for autonomy*, refers to the patient's right to self-rule, free from interference from others or from inadequate understanding of clinical choices. In the context of this chapter, respect for autonomy pertains chiefly to treatment involving prescribed and nonprescribed controlled substances.

With regard to the former, it involves discussions about the risks, benefits, costs, and alternatives associated with the use of medications and the rationale for the use of drug testing as one component of monitoring the safety and effectiveness of their administration. Such discussions typically are codified in the form of an informed consent document, a medication treatment agreement, or both. These documents should memorialize, but not substitute for, a conversation between the clinician and the patient.

With regard to drug testing, the conversation should include the details of testing protocols, including the testing schedule (random, scheduled, or for-cause) and testing matrices (urine, oral fluid, or hair), but should not include disclosure of the composition of the test panel, as this would undermine the deterrent effects of drug testing. In the case of urine, the discussion should include methods of collection (unmonitored, monitored, directly observed) and behaviors that would trigger monitored or observed collections, consequences of refusal to test, and clinical actions that may be taken in response to inappropriate test results. Reasonable actions might include instituting closer follow-up and otherwise enhancing treatment boundaries, involving family in the care plan, modifying the treatment plan, or referring the patient to an addiction specialist for evaluation and management of his or her substance use disorder. Provisions stipulating that failed drug test results will result in patient dismissal will effectively foreclose patient disclosures about their substance use and have no legitimate medical or ethical basis (76).

Ultimately, some patients will not agree to such informed consent or treatment agreements or, if they do agree, will subsequently refuse a test. Again, this should prompt discussion, but if the issue cannot be resolved, further controlled substance prescribing generally will be contraindicated. In its place, the clinician should design a therapeutic plan without controlled substances or refer the patient elsewhere for care (76).

which to evaluate the efficacy of opioid therapy as well as reflect outcomes that are meaningful to the patient. Functional goals might include, for example, measurable improvement in valued activities such as taking a daily walk of a certain duration, concentrating on reading for a specific period of time, or sitting through a church service or a movie.

Discussion of risks should be individualized based on the patient's history and comorbidities. Among potential risks commonly considered and cited in the informed consent portion of the OTA are

- Physical side effects (eg, nausea, itching, constipation, sweating)
- CNS side effects (eg, sedation, cognitive clouding, euphoria)
- Respiratory effects (eg, shallow breathing, decreased breathing rate, overdose and death)
- Endocrine effects (eg, low testosterone, amenorrhea, osteopenia)
- Physiological dependence and tolerance
- Hyperalgesia, increased pain
- Morbidity/mortality possible with unhealthy opioid use (including children and adolescents in the home)
- Substance use disorder
- Risk of victimization (manipulation, theft, assault to obtain opioids)

In addition, the recent CDC and VA/DoD guidelines suggest that discussion of naloxone use for overdose reversal be included in the informed consent component of the agreement (48,49), although no studies are available of outcomes related to naloxone prescribing to persons using opioids for analgesia. A small survey study of veterans on long-term opioids for pain indicated that they underestimated their risk for opioid overdose (286). Importantly, 21% reported having previously experienced an opioid overdose, and most desired a naloxone rescue kit to enhance their safety (287).

Documentation of the plan of care is critical because opioids are subject to unhealthy use and diversion, with the potential for harm to the patient and the public (288). Typically, the plan of care includes such details as the following:

- Management of medications, such as
  - Use of a single provider (or practice) in charge of prescriptions
  - Which pharmacy will fill
  - Process for dose/frequency changes; avoidance of self-initiated changes
  - Keeping medications secure without sharing
  - Frequency of appointments and urine toxicology testing for use of illicit substances and to confirm presence of prescribed substances
- Expected other pain treatment activities, for example:
  - Attending cognitive–behavioral groups
  - Physical therapy
  - Exercising independently
  - Meditation/deep relaxation
- Expected participation in treatment for substance use disorders, for example:
  - AA or NA meetings
  - Counseling
  - Psychiatric care
- Avoidance of illicit or nonprescribed substances, alcohol, and prescribed CNS depressants in particular benzodiazepines
- Conditions under which opioids will be continued
  - Improvement in pain
  - Increased function
  - Ability to adhere generally to the plan of care
- Condition under which opioids will be discontinued
  - Lack of progress toward goals of treatment
  - Unsafe use of medications or harmful side effects

Urine Drug Monitoring

Urine drug testing (UDT) includes UDS and confirmatory testing for unexpected or irregular results on UDS. Toxicology testing is nowadays considered routine prior to initiating opioid therapy and as part of long-term opioid treatment in order to document use of the prescribed medication and to identify use of illicit or nonprescribed substances. UDT can provide objective information, especially important in patients with SUDs who may be unable or unwilling to share accurate information and have difficulty controlling their medication use (289). An analysis within the VHA showed that veterans on long-term opioid therapy receiving care at facilities with more frequent ordering of urine drug screens had lower risk of suicide attempts (290). It is critical that clinicians take care in interpreting the results of the screen and using them to advance the care of patients. Most screening tests are immunoassays that can have false positives due to cross-reaction with other drugs and false negatives due to lack of reactivity to some opioids and sensitivities that are too low to detect low blood levels. Some panels do not test for a wide enough range of opioids, especially synthetics and semisynthetics; thus, certain opioids of concern to the provider will need to be separately added for testing. Drug screening panels differ in the drugs that are detected. Therefore, unexpected findings on a screening test should prompt confirmation usually by liquid or gas chromatography coupled with mass spectroscopy (291,292).

Toxicology screens should be approached in a patient-centered way and can provide support for recovery in persons with addiction. Unexpected finding should trigger a discussion with the patient and lead to enhanced treatment of the individual depending on the reason for the finding (292). Care may need to be revised or changed, but toxicology results should be understood as a single point of information among many in the rich array of information the clinician has regarding the patient.

In persons with no appreciated special risks for unhealthy medication use and no aberrant behaviors, toxicology testing is done randomly at a minimum of annual basis by many experts, though a recent expert consensus panel funded by a urine toxicology testing company recommended more frequent routine screening (293). For persons at higher risk, testing should be done more often, such as monthly or even more than weekly, especially during periods of high stress (49).

of physical tolerance and thus is an important contributor to patient safety.

Therapeutic drug testing also is a necessary part of long-term prescribing of controlled medications. It is the single most useful laboratory test to monitor adherence to the treatment plan, as well as to detect the use of nonprescribed drugs and alcohol (49,50). Drug testing is an important monitoring tool because patients' self-reports of medication use can be unreliable and behavioral observations may detect some problems but not others (51). Using drug testing when prescribing controlled drugs is essentially the same as following glycosylated hemoglobin levels when managing diabetes. However, physicians need to be aware of the limitations of available tests (such as their limited sensitivity for many opioids) and take care to order tests appropriately (49,52). Because of the complexities involved in interpreting drug test results, it is advisable to verify significant or unexpected results through confirmatory studies and consultation with the testing laboratory's toxicologist or a clinical pathologist (49,50).

Test results that suggest possible nonmedical use of the prescribed medication or other drugs should be discussed with the patient. It is helpful to approach such a discussion in a positive, supportive manner, so as to strengthen the physician–patient relationship and encourage healthy behaviors (as well as behavioral changes where needed). Both the test results and subsequent discussion with the patient should be thoroughly documented in the medical record (49).

Whenever the physician is concerned about a patient's behavior or clinical progress (or the lack thereof), it is advisable to seek a consultation with an expert in the disorder for which the patient is being treated. If there is concern about possible medication nonmedical use or diversion, consultation with an expert in addiction medicine also is advised. Physicians place themselves and their patients at risk if they continue to prescribe controlled medications in the presence of concerning patient behaviors, and addiction specialty consultation can be very helpful in protecting both the patient and physician.

Based on the Patient's Response, Decide Whether to Continue, Revise, or Terminate Medication Therapy

No treatment regimen should be left open-ended. Throughout the course of therapy, the physician and patient should regularly weigh the potential benefits and risks of continued treatment and determine whether such treatment remains appropriate (32,45). Continuation, modification, or termination of medication therapy should be contingent on *both* (a) evidence of the patient's progress toward the established treatment objectives *and* (b) the absence of substantial risks or adverse events (53–55) (see Table 117-1).

A satisfactory response to treatment would be indicated by reduced severity of symptoms, increased level of function, and/or improved quality of life (41) in the absence of dangerous or

TABLE 117-1 Identifying and Responding to Nonmedical Prescription Medication Use

Term	Definition	Clinical Examples	Intervention Strategies
Appropriate Use	Use of a controlled substance as prescribed for a defined condition with no signs of nonmedical use or substance use disorder.	A 10-day course of postoperative opioids, taken as prescribed.	Explain in advance to the patient that opioids will be used for only a limited time.
Nonmedical Use	Use of a controlled substance for a reason other than that for which it was prescribed or in a dosage different than that prescribed. No pattern of misuse leading to disability or dysfunction.	A single episode of an opioid used twice as often as prescribed.Use of an old prescription for a new clinical problem without consulting a physician.	Educate the patient about proper use of the medication.
Prescription Medication Use Disorder	Use of a controlled substance outside the normally accepted standards of use, resulting in disability and/or dysfunction, and meeting DSM-5 criteria for a substance use disorder.	Continued nonmedical use despite interventions.Use of an opioid for recreational purposes unrelated to a medical condition.	Express concern in an empathic manner.Discontinue the medication.Consult with an expert (eg, on addiction or pain management).
Catastrophic Use	Use of a controlled substance in a manner that involves illegal activity or places the patient at risk of immediate harm.	Altering a prescription or selling a controlled substance.Overdose of a controlled substance.	Immediately stop prescribing any controlled substances. Consult with an expert in addiction medicine or addiction psychiatry.Notify legal authorities if indicated.

Source: Data adapted from Isaacson JH, Hopper JA, Alford DP, et al. Prescription drug use and abuse: risk factors, red flags, and prevention strategies. *Postgrad Med*. 2005;118:19.

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A Review of Buprenorphine Diversion and Misuse: The Current Evidence Base and Experiences from Around the World

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Abstract

Outpatient opioid addiction treatment with sublingual buprenorphine pharmacotherapy (OBOT) has rapidly expanded in the United States and abroad, and, with this increase in medication availability, there have been increasing concerns about its diversion, misuse and related harms. This narrative review defines the behaviors of diversion and misuse, examines how the pharmacology of buprenorphine alone and in combination with naloxone influence its abuse liability, and describes the epidemiological data on buprenorphine diversion and intravenous misuse, risk factors for its intravenous misuse and the unintended consequences of misuse and diversion. Physician practices to prevent, screen for, and therapeutically respond to these behaviors, which are a form of medication non-adherence, are discussed and gaps in knowledge are identified. OBOT experiences from other countries that have varied health care systems, public policies, and access to addiction treatment are shared in order to make clear that diversion and misuse occur across the world in various contexts, for many different reasons, and are not limited to buprenorphine. Comparisons are made with other opioids with known abuse liability as well as medications with no known abuse. The objective is to facilitate understanding of diversion and misuse so that all factors influencing their expression (patient and provider characteristics and public policy) can be appreciated within a framework that also recognizes the benefits of addiction treatment. With this comprehensive perspective, further careful work can help determine how to minimize these behaviors without eroding the current benefits realized through improved addiction treatment access and expansion.

Keywords

buprenorphine; misuse; diversion; treatment; epidemiology; behavioral pharmacology

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decreasing relapse, one must become interested also in medication adherence. Thus, assessment for misuse and diversion is recommended at each clinical visit with placement of these behaviors on patients' problem list so they can be addressed therapeutically, rather than punitively.

A punitive "no tolerance" approach with automatic discharge from treatment is highly unlikely to help patients because untreated opioid addiction is characterized by relapse [continued use of illicit (i.e., diverted) opioids is the norm] and increased morbidity and mortality (McLellan et al., 2000). Good treatment benefits both individual and public health even when patients are unable to achieve continuous drug abstinence and cessation from all criminal activity and IVDU (National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction, 1998; Carrieri et al., 2006). For example, a recent study compared three groups of injection drug users receiving needle-exchange services in Norway: 1) persons currently in addiction treatment with methadone or buprenorphine (n=341); 2) persons with no prior treatment with these medications (n=1063); and 3) persons who had prior, but not current, treatment with these medications (n=356). Those currently in treatment, despite continued IVDU, had significantly fewer non-fatal overdoses (O.R.=0.5), committed fewer thefts (O.R.=0.6) and reported dealing drugs (O.R.=0.7) less often in the prior month. They were also less likely to use heroin daily or near daily (O.R.=0.3) compared to the other groups that were not in treatment (Gjersing and Bretteville-Jensen, 2013). This does not imply that physicians must accept and do nothing about medication misuse and diversion or that they should continue to prescribe buprenorphine to patients who are distributing it to others rather than taking it themselves. Rather, the point is that treatment can be beneficial even if the ideal outcome is not attained (e.g., 100% medication adherence and abstinence from all substances of abuse). The goal is to evaluate treatment benefits and harms for each patient, individualizing the treatment plan in order to minimize harms without adversely affecting the benefits provided.

Reasons for buprenorphine diversion and misuse while in OBOT are listed in Table 1. Once providers understand the context and circumstances around these behaviors, practical solutions can be formulated. For instance, for a patient who encounters drug dealers every month at the pharmacy where they fill their prescription and are pressured to sell their medication, a recommendation to change pharmacies and assistance with finding financial help may be welcome if the medication is being sold to pay off old debts. For patients unable to escape from drug-addicted social networks, it may be helpful to discuss the option of maintaining a secretive status regarding having medication (Havnes et al., 2013).

Patients may not disclose medication misuse and diversion; however, some clinical practice behaviors (see Table 2), such as monitoring urine drug test outcomes, including for buprenorphine, are recommended and may be helpful. Inexpensive CLIA-waived urine tests for buprenorphine are now readily available in the U.S. In a cross-sectional study in India, 14% and 34% of patients receiving BUP/NX and BUP, respectively, tested negative for buprenorphine on random observed urine testing (Balhara and Jain, 2012). A test that is positive for buprenorphine but negative for its primary metabolite, norbuprenorphine, would also be incongruent with daily medication use. Admittedly, urine drug testing has limited practical use in detecting intermittent non-adherence due to the long half-life of

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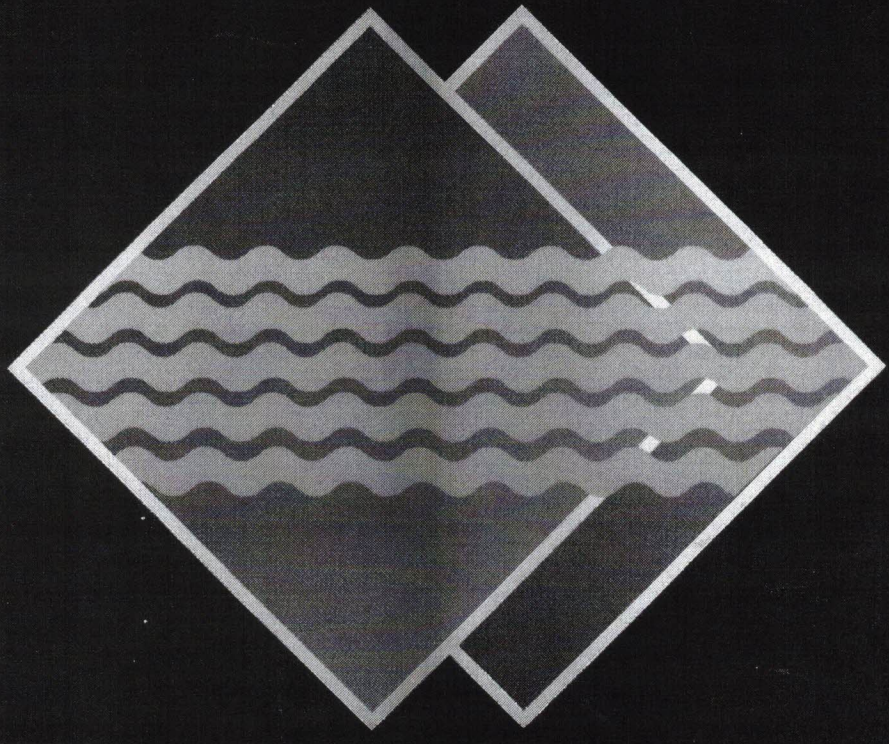

Gerald M. Aronoff

is a high level of concern about such behaviors, monitoring may require relatively frequent visits, regular assessment of significant others who can provide observations about patients' drug use, and periodic urine drug screens.

Urine drug screening can facilitate the early recognition of aberrant drug-related behaviors in patients who have been actively abusing drugs in the recent past. Urine should be screened for both illicit and licit but unprescribed drugs. The patient should be fully informed about this approach, which should be explained as a method of monitoring that can be reassuring to the clinician and thereby facilitate aggressive symptom-oriented treatments. The patient should also be apprised of the clinician's response to positive screens. This response usually entails increasing the monitoring procedures for continued treatment, including greater frequency of visits, smaller quantities of prescribed drugs, and so on. In the case of repeated violations, referral for concurrent drug rehabilitation may be the most appropriate course. If the abuse is extreme, ongoing analgesic treatment cannot be justified.

In some cases the approach to monitoring may best be accomplished through the use of a written contract. This contract, which is kept in the medical record, defines the drug regimen, explicitly states the responsibilities of both the patient and the clinician, and stipulates the consequences of aberrant drug use. These guidelines should include specific reference to the methods that will be used to renew prescriptions and the response to the report of lost or stolen drugs.

Patients who protest the use of urine drug screens or contracts may be unwilling or unable to enter a collaborative relationship in which the clinician can be confident of responsible drug taking by the patient and the patient can be confident that the clinician will respond to unrelieved symptoms with aggressive therapies. Such patients may not be candidates for treatment with abusable drugs.

Other Aspects of Patient Monitoring and Education

Patients must be given detailed instructions about the parameters of responsible drug taking. The goal is to prevent the use of illicit drugs, if possible, and to eliminate abuse of the prescribed drug regimen. Patients suspected of aberrant drug use must be seen frequently. Weekly visits are common initially. Frequent visits help establish close ties with staff, allow evaluation of both symptom control and addiction-related concerns, and allow the prescription of small quantities of drugs, which may diminish the temptation to misuse and provide an incentive for keeping appointments.

For patients who are considered to be at high risk for aberrant behavior, the clinician's response to "lost" prescriptions, requests for early refills, and other aberrant behaviors should be decided in advance, to the extent possible, and clearly explained to the patient. There can be no prescription renewals if appointments are missed. The patient should be told that dose changes require prior contact with the clinician or designee. It may be useful to reassure the patient that dose escalation of drugs used for symptom control is common and acceptable, if the clinical evaluation supports this course and the patient deals with the need for a change in drug regimen without relying on aberrant behaviors.

The rigidity of the plan to deal with "lost" prescriptions or the need for early refills due to unsanctioned dose escalation again depends on the clinician's assessment of the degree of abuse. In some cases, it is appropriate to stipulate at the outset that early refills for prescription loss will not be provided unless the patient presents a police report that documents the event. In other cases, it may be sufficient to inform the patient that the behavior is unacceptable and may lead to an inability to provide uninterrupted treatment. Subsequent decisions about the response to aberrant behavior can then be based on observation of the patient's response to these guidelines.

To avoid conflicts after hours or during holiday periods, clinicians who cover for the primary care giver must be informed about the guidelines that have been established for each patient with a history of abuse. Again, the restrictions should be made more or less stringent based on the level of concern about aberrant behaviors.

Some patients are so concerned about the potential for addiction or readdiction that compliance with therapy is threatened. It is ironic that some patients actually prefer rigid guidelines because of an enhanced sense of control over drugs. In discussing the need for compliance, it is also important to have the patient realize that there is a risk of readdiction associated with uncontrolled pain or other symptoms. Counseling can also help patients identify possible triggers to drug and alcohol abuse that they may encounter during treatment and develop strategies for avoiding illicit drug use or uncontrolled use of prescribed drugs at those times.

Treatment of Comorbid Psychiatric Disorders

Psychiatric comorbidity, including personality disorders (e.g., borderline, antisocial), depression, and anxiety disorders, is relatively high in patients with substance abuse histories (28). The treatment of anxiety and depression can increase the patient's comfort and possibly diminish the likelihood of relapse. For these reasons, early psychiatric consultation should be considered when significant psychiatric impairment is observed.

The Role of Drug Recovery Programs

Some patients can be referred to a drug recovery program as a means to curtail drug abuse during treatment for pain. Patients can document their attendance at groups to further reassure the clinician about the effort to comply with therapy. Patients who enter a program and are given a sponsor may allow the physician or designee to contact the sponsor, who may also help support the clinical plan. This type of contact also helps to prevent the patient's ostracism by others in the program if controlled prescription drugs are needed.

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ASIPP - Opioid Guidelines 2012

American Society of Interventional Pain Physicians (ASIPP) Guidelines for Responsible Opioid Prescribing in Chronic Non-Cancer Pain: Part 2 - Guidance

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Results:

Part 2 of the guidelines on responsible opioid prescribing provides the following recommendations for initiating and maintaining chronic opioid therapy of 90 days or longer.

1. A) Comprehensive assessment and documentation is recommended before initiating opioid therapy, including documentation of comprehensive history, general medical condition, psychosocial history, psychiatric status, and substance use history. (Evidence: good)
   B) Despite limited evidence for reliability and accuracy, screening for opioid use is recommended, as it will identify opioid abusers and reduce opioid abuse. (Evidence: limited)
   C) Prescription monitoring programs must be implemented, as they provide data on patterns of prescription usage, reduce prescription drug abuse or doctor shopping. (Evidence: good to fair)
   D) Urine drug testing (UDT) must be implemented from initiation along with subsequent adherence monitoring to decrease prescription drug abuse or illicit drug use when patients are in chronic pain management therapy. (Evidence: good)
2. A) Establish appropriate physical diagnosis and psychological diagnosis if available prior to initiating opioid therapy. (Evidence: good)
   B) Caution must be exercised in ordering various imaging and other evaluations, interpretation and communication with the patient; to avoid increased fear, activity restriction, requests for increased opioids, and maladaptive behaviors. (Evidence: good)
   C) Stratify patients into one of the 3 risk categories – low, medium, or high risk.
   D) A pain management consultation, may assist non-pain physicians, if high-dose opioid therapy is utilized. (Evidence: fair)
3. Essential to establish medical necessity prior to initiation or maintenance of opioid therapy. (Evidence: good)
4. Establish treatment goals of opioid therapy with regard to pain relief and improvement in function. (Evidence: good)
5. A) Long-acting opioids in high doses are recommended only in specific circumstances with severe intractable pain that is not amenable to short-acting or moderate doses of long-acting opioids, as there is no significant difference between long-acting and short-acting opioids for their effectiveness or adverse effects. (Evidence: fair)
   B) The relative and absolute contraindications to opioid use in chronic non-cancer pain must be evaluated including respiratory instability, acute psychiatric instability, uncontrolled suicide risk, active or history of alcohol or substance abuse, confirmed allergy to opioid agents,

Table 2 (cont.). *Drug cross-reactants.*

Drug Group	Cross Reactivity Based on Product Insert	Cross Reactivity Based on Potential Cross-Reaction
Barbiturates	Alphenal	Phenytoin (Dilantin) Primidone (Mysoline)
Oxycodone	Hydrocodone Hydromorphone (Dilaudid) Oxymorphone (Numorphan) Codeine (Codeine)	

Source: DrugCheck® Cross Reactivity Chart (www.drugcheck.com/_images/DC145_Cross-Reactivity_chart.pdf)

Table 3. *Interpreting unexpected results of urine drug screens.*

	Unexpected Result	Possible Explanations	Actions for the Physician
1	UDS negative for prescribed opioid.	• False negative. • Non-compliance. • Diversion.	• Repeat test using chromatography; specify the drug of interest (e.g. oxycodone often missed by immunoassay). • Take a detailed history of the patient's medication use for the preceding 7 days (e.g., could learn that patient ran out several days prior to test). • Ask patient if they've given the drug to others. • Monitor compliance with pill counts.
2	UDS positive for non-prescribed opioid or benzodiazepines.	• False positive. • Patient acquired opioids from other sources (double doctoring, "street").	• Repeat UDS regularly. • Ask the patient if they accessed opioids from other sources. • Assess for opioid misuse/addiction. • Review/revise treatment agreement.
3	UDS positive for illicit drugs (e.g., cocaine, cannabis).	• False positive. • Patient is occasional user or addicted to the illicit drug. • Cannabis is positive for patients taking dronabinol (Marinol®), THC:CBD (Sativex®) or using medical marijuana.	• Repeat UDS regularly. • Assess for abuse/addiction and refer for addiction treatment as appropriate. • Ask about medical prescription of dronabinol, THC:CBD or medical marijuana access program.
4	Urine creatinine is lower than 2–3 mmol/liter.	• Patient added water to sample.	• Repeat UDS. • Consider supervised collection or temperature testing. • Take a detailed history of the patient's medication use for the preceding 7 days. • Review/revise treatment agreement.
5	Urine sample is cold.	• Delay in handling sample (urine cools within minutes). • Patient added water to sample.	• Repeat UDS, consider supervised collection or temperature testing. • Take a detailed history of the patient's medication use for the preceding 7 days. • Review/revise treatment agreement.

UDS=urine drug screen; THC=Tetrahydrocannabinol; CBD=cannabidiol

Source: Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain© 2010 National Opioid Use Guideline Group (NOUGG) (54).

ing fail to detect problems with drug misuse and abuse (53). Creating a UDT policy that is applicable universally and consistently with all patients assists to "de-stigmatize" UDT and can potentially convince patients that it has nothing to do with an individual patient or their trustworthiness (53,54). Consequently, the practice can explain to patients that drug testing is a routine procedure for all patients starting or maintained on opioid therapy and it is an important tool for monitoring the safety of opioid therapy. The UDT not only provides adherence monitoring, but it is also a monitoring tool for safety.

- As it is very difficult to correlate urine drug concentration with a patient's dose, it is not feasible for the physician to ascertain whether or not a patient has taken the dose of opioid appropriately using UDT. UDT can, however, detect the parent drug and/or its metabolites and demonstrate recent use of prescribed drugs and illegal substances. UDT will

VA/DoD CLINICAL PRACTICE GUIDELINE FOR OPIOID THERAPY FOR CHRONIC PAIN

Department of Veterans Affairs

Department of Defense

QUALIFYING STATEMENTS

The Department of Veterans Affairs and the Department of Defense guidelines are based upon the best information available at the time of publication. They are designed to provide information and assist decision making. They are not intended to define a standard of care and should not be construed as one. Neither should they be interpreted as prescribing an exclusive course of management.

This Clinical Practice Guideline is based on a systematic review of both clinical and epidemiological evidence. Developed by a panel of multidisciplinary experts, it provides a clear explanation of the logical relationships between various care options and health outcomes while rating both the quality of the evidence and the strength of the recommendation.

Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every healthcare professional making use of these guidelines is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation.

These guidelines are not intended to represent TRICARE policy. Further, inclusion of recommendations for specific testing and/or therapeutic interventions within these guidelines does not guarantee coverage of civilian sector care. Additional information on current TRICARE benefits may be found at www.tricare.mil or by contacting your regional TRICARE Managed Care Support Contractor.

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- **Co-administration of a drug capable of inducing fatal drug-drug interactions:** Providers should carefully rule out and avoid potential drug interactions prior to initiating LOT. For example, the following combinations are dangerous:[66]
  - Opioids with benzodiazepines (compared to patients with no prescription, the odds ratio [OR] and 95% confidence interval [CI] for drug-related death was OR: 14.92, 95% CI: 7.00-31.77 for patients who filled a prescription for opioids and benzodiazepines; OR: 3.40, 95% CI: 1.60-7.21 for patients who filled only an opioid prescription, and 7.21, 95% CI: 3.33-15.60 for patients who filled only a benzodiazepine prescription) (see Recommendation 5) [66,67]
  - Fentanyl with CYP3A4 inhibitors
  - Methadone with drugs that can prolong the QT interval (the heart rate's corrected time interval from the start of the Q wave to the end of the T wave) (e.g., CYP450 2B6 inhibitors)
- **QTc interval >450 ms for using methadone:** Unlike most other commonly used opioids, methadone has unique pharmacodynamic properties that can prolong the QTc interval (the heart rate's corrected time interval from the start of the Q wave to the end of the T wave) and precipitate torsades de pointes, a dangerous or fatal cardiac arrhythmia. Patients who may be at risk include those with other risk factors for QTc prolongation, current or prior electrocardiograms (ECGs) with a prolonged QTc >450 ms, or a history of syncope. Therefore, ECGs before and after initiating methadone are highly advised (see Methadone Dosing Guidance).
- **Evidence for or history of diversion of controlled substances:** The clinician should communicate to patients that drug diversion is a crime and constitutes an absolute contraindication to prescribing additional medications. Because suspicion is subjective and may be based on impression, bias, or prejudice, it is important that providers who suspect diversion base treatment plans on objective evidence. Suspicions may be confirmed by a negative mass spectrometry/liquid chromatography UDT for the substance being prescribed in the absence of withdrawal symptoms in someone who is receiving opioids. A negative UDT for the prescribed opioid could also by itself be a sign of diversion. Signs of diversion may also include frequent requests for early refills or atypically large quantities required to control pain. Routine UDT, however, may not reliably detect synthetic opioids (e.g., methadone, fentanyl, tramadol) or semi-synthetic opioids (e.g., oxycodone, hydrocodone, hydromorphone). When there is evidence that the patient is diverting opioids, discontinue opioids according to Recommendations 14 and 15 and assess for underlying OUD and/or psychiatric comorbidities. Consultation with a pain specialist, psychiatrist, or SUD specialist may be warranted. Also consider consultation with local risk management and/or counsel. For patients with OUD, keep in mind that sudden discontinuation of opioids due to suspected diversion may place them at high risk for illicit opioid use and resulting opioid overdose (see Recommendation 17).
- **Intolerance, serious adverse effects, or a history of inadequate beneficial response to opioids:** Serious harm may occur should patients be prescribed additional (or different) opioids if prior administration of opioids led to serious adverse effects or was not tolerated. It is also inadvisable to prescribe opioids to patients who already have had an adequate opioid trial (of